ELSEVIER

European Journal of Pharmacology 387 (2000) 59–62

ejp

www.elsevier.nl/locate/ejphar

Short communication

Comparison of noncontingent versus contingent cocaine administration on plasma corticosterone levels in rats

Ruggero Galici [a], Robert N. Pechnick [a,b,*], Russell E. Poland [c], Charles P. France [a,b]

[a] *Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center, 1100 Florida Avenue, New Orleans, LA 70119-2799, USA*

[b] *Neuroscience Center of Excellence, Louisiana State University Health Sciences Center, 1100 Florida Avenue, New Orleans, LA 70119-2799, USA*

[c] *Cedars Sinai Medical Center, Thalians Mental Health Center, Department of Psychiatry, Los Angeles, CA 90048, USA*

Received 27 October 1999; accepted 2 November 1999

Abstract

The purpose of the present study was to compare the effects of contingent and noncontingent cocaine administration on plasma levels of corticosterone in rats. Male rats were trained to self-administer cocaine under a fixed-ratio 5 schedule. The rats were yoked such that the delivery of cocaine (0.25 mg/kg/infusion) to one rat (contingent cocaine) produced the simultaneous noncontingent delivery of the same dose of cocaine (noncontingent cocaine) or saline (noncontingent saline) to other rats. Although saline administration had no effect, plasma corticosterone levels were significantly higher in rat receiving contingent cocaine compared to those receiving noncontingent cocaine. These results demonstrate that the active vs. passive administration of cocaine can differentially affect this neuroendocrine response.

Keywords: Cocaine; Corticosterone; Neuroendocrine; Hypothalamo pituitary–adrenal axis; Self-administration; Stress

1. Introduction

Cocaine can affect neuroendocrine function in a number of species (Borowsky and Kuhn, 1991; Mendelson et al., 1992; Sarnyai et al., 1995). Studies have shown that the acute administration of cocaine stimulates the hypothalamo–pituitary–adrenal axis, producing rapid and short-lived increases in plasma levels of adrenocorticotrophic hormone (ACTH) and corticosterone in rats (Borowsky and Kuhn, 1991). Although cocaine does not have direct effects at the level of either the pituitary (Rivier and Vale, 1987) or the adrenal (Krueger et al., 1991) gland, it does stimulate the secretion of corticotropin-releasing factor (CRF) from hypothalamic explants (Calogero et al., 1989). Moreover, increases in plasma corticosterone levels have been observed in rats after the acute intracerebroventricular or intrahypothalamic injection of cocaine (Saphier et al., 1993). These data suggest that the effects of cocaine on the hypothalamo–pituitary–adrenal axis are centrally mediated in rats.

Although it is clear that cocaine stimulates the hypothalamo–pituitary–adrenal axis, the importance of the contingencies of drug delivery has not been established. Studies examining other functional endpoints have demonstrated that there are differences between the effects of active and passive administration of cocaine. For example, it has been shown that mortality is higher in rats receiving cocaine noncontingently compared to rats self-administering cocaine (Dworkin et al., 1995b). Moreover, there are differences in neurotransmitter levels (Wilson et al., 1994; Hemby et al., 1997) and neurotransmitter turnover rates during withdrawal (Dworkin et al., 1995a) between rats receiving cocaine contingently vs. noncontingently. The purpose of the present study was to test the hypothesis that the active (response contingent) vs. passive (response noncontingent) administration of cocaine differentially affects the hypothalamo–pituitary–adrenal axis.

* Corresponding author. Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center, 1100 Florida Avenue, New Orleans, LA 70119-2799, USA. Tel.: +1-504-619-8794; fax: +1-504-619-8706.

E-mail address: rpechn@lsumc.edu (R.N. Pechnick)

0014-2999/00/$ - see front matter
PII: S0014-2999(99)00780-3

2. Material and methods

Twenty-seven male Sprague–Dawley derived rats (250–300 g, Charles River, Wilmington, MA) were housed individually in stainless steel cages and maintained under a 12/12 h light/dark cycle (lights on 07:00–19:00 h). All rats were initially trained to respond for food pellets. Access to food was restricted in order to maintain the rats at 85–90% of their free-feeding weight. Every day, beginning 3 days after arrival, the rats were placed into ventilated, sound attenuating operant chambers that were equipped with stimulus lights and response levers. Initially, the rats were trained to respond under a continuous reinforcement schedule of food presentation. When lever pressing under the continuous reinforcement schedule became reliable, a fixed ratio (FR) reinforcement schedule was initiated. The FR response requirement was increased by one response per session until a terminal response requirement of 5 (FR 5) was achieved.

After the completion of food training, a chronic indwelling i.v. jugular catheter was implanted for drug administration and blood sampling as described previously (Emmett-Oglesby et al., 1993). The rats were anesthetized with a cocktail of chlordiazepoxide (10.68 mg/kg), ketamine (53.28 mg/kg) and nalbuphine (1.32 mg/kg) administered i.p. An indwelling silastic catheter (0.015 inch o.d.) connected to a 22-gauge guide cannula (Plastic One, Roanoke, VA) was inserted into the jugular vein. The cannula was tunneled subcutaneously to the back of the head, exteriorized, and fixed to the skull with jewelers screws and Cranial Plast Cement (Plastics One, Roanoke, VA). The cannula and catheter was filled with heparinized saline (20 units/ml) and sealed with a dummy cannula. Immediately after surgery and twice daily thereafter, the cannula was flushed with sterile heparinized saline (20 units/ml), streptokinase (1700 units/ml) and ticarcillan (14 mg/ml).

The rats were randomly assigned to treatment groups. Rats that self-administered cocaine hydrochloride (contingent cocaine; 0.25 mg/kg/infusion) were yoked to separate groups of rats that received a non-contingent infusion of either the same dose of cocaine (noncontingent cocaine) or saline (noncontingent saline). The noncontingent cocaine rats had never received contingent cocaine. In the rats receiving contingent cocaine, 5 responses on the active lever resulted in the delivery of cocaine or saline solution followed by a 30 s timeout. The infusion duration was 4–5 s, corresponding to the delivery of 80–100 μl. The sessions ended after 20 infusions or 60 min, whichever occurred first. Blood samples (200 μl) were withdrawn 1 min before and immediately after each experimental session using the same jugular catheter through which cocaine or saline was administered. The blood was collected into iced heparinized minivials, centrifuged for 3 min at 15,000 rpm, and aliquots of plasma were frozen at −70°C. Plasma corticosterone levels were detected by radioimmunoassay using corticosterone antiserum as previously described (Pechnick and Poland, 1994). The limit of sensitivity for the assay was 2.0 ng/ml, and the maximum inter- and intra-assay coefficients of variation for the corticosterone assay were 14% and 10%, respectively. All samples were analyzed in duplicate. Although plasma corticosterone samples were collected across several sessions in some rats, data from individual subjects did not show any systematic changes over time.

Differences across the treatment groups before and after the sessions first were assessed by two-way, repeated measures analysis of variance (ANOVA). One-way ANOVA followed by Scheffe's tests were used to compare each treatment before and after the session, and paired t tests were used to compare before and after session values within each treatment group. Data from all subjects within a group were averaged and presented as means ± S.E.M. The criterion for the rejection of the null hypothesis was $P < 0.05$.

3. Results

When cocaine was available, rats received 19 ± 0.5 infusions per session. Repeated measures ANOVA showed significant treatment [$F(2,91) = 4.2$, $P = 0.018$] and time [$F(1,91) = 31.7$, $P = 0.0001$] effects (Fig. 1). Before the experimental sessions, plasma corticosterone levels were not significantly different among the three groups [$F(2,91) = 0.6$, $P = 0.5698$], but there were significant post-session differences [$F(2,91) = 5.7$, $P < 0.0045$]. Noncontingent saline administration had no effect on plasma corticosterone levels. Noncontingent cocaine administration produced a slight, though statistically significant increase in plasma corticosterone compared to baseline levels (88.6 ng/ml vs. 117.1 ng/ml). Contingent cocaine produced a much greater increase in plasma corticosterone (97.3 vs.

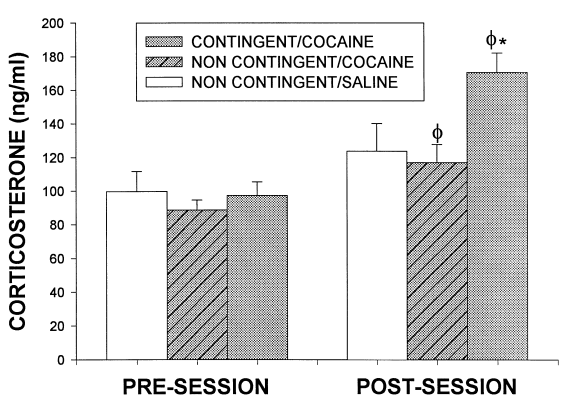

Fig. 1. Plasma corticosterone concentration measured immediately before and after the experimental session among three different groups: contingent cocaine (0.25 mg/kg/infusion, i.v.); noncontingent cocaine (0.25 mg/kg/infusion, i.v.) and noncontingent saline. $^{\phi}P < 0.05$ compared to pre-session value; $^{*}P < 0.05$ compared to noncontingent and saline-treated subjects; $N = 20–44$/group.

170.6 ng/ml), and plasma corticosterone levels were significantly higher in rats receiving contingent cocaine compared to those receiving noncontingent cocaine.

4. Discussion

Intravenous drug self-administration is a behavioral procedure that has been used mainly to measure the reinforcing effects of drugs; however, the present study utilized this methodology to study the effects of contingent and noncontingent cocaine administration on plasma levels of corticosterone in rats. Both contingent and noncontingent administration of cocaine (0.25 mg/kg/infusion) significantly increased plasma corticosterone from baseline levels. The maximal number of infusions per session (19 ± 0.5) at this dose resulted in the i.v. administration of approximately 4.75 mg/kg over the experimental session. This dose is lower than that required to increase plasma corticosterone levels in the rat after i.p. (noncontingent) administration (Borowsky and Kuhn, 1991). Although it is not unexpected that there would be differences in drug response after i.v. compared to i.p. drug administration due to pharmacokinetic factors, part of the difference might be due to the contingencies of drug administration. Supporting this hypothesis is the finding that plasma corticosterone levels were significantly higher in rats receiving contingent cocaine compared to those receiving the same dose of cocaine in a noncontingent manner.

Cocaine can stimulate the hypothalamo–pituitary–adrenal axis by acting directly at the level of the hypothalamus (Calogero et al., 1989; Saphier et al., 1993). The differences between contingent and noncontingent cocaine administration found in the present study suggest that there are other, less direct mechanisms involved in the response of the hypothalamo–pituitary–adrenal axis after self-administered drug. For example, increases in locomotor activity associated with lever pressing, or general arousal might contribute to the activation of the hypothalamo–pituitary–adrenal axis. Differences in the responses to contingent and noncontingent cocaine have been reported by others (Wilson et al., 1994; Dworkin et al., 1995a,b; Hemby et al., 1997).

Although it is apparent that both contingent and noncontingent cocaine administration can activate the hypothalamo–pituitary–adrenal axis, the relationship between the activation of the hypothalamo–pituitary–adrenal axis and the reinforcing effects of cocaine has not been completely elucidated. There are data indicating that corticosterone plays an important role in cocaine self-administration. Footshock (Goeders and Guerin, 1994) and social stress (Haney et al., 1995) can stimulate the hypothalamo–pituitary–adrenal axis and facilitate the acquisition of cocaine self-administration. Moreover, Deroche et al. (1993) found that exogenously administered corticosterone promotes the reinstatement of cocaine self-administration. The increased activation of the hypothalamo–pituitary–adrenal axis associated with the contingent administration of cocaine might contribute to the acquisition, maintenance and reinstatement of self-administration behavior.

The dose that was used in this study was selected based upon the results of a dose–response experiment showing that it produced a maximum number of infusions per session. As plasma corticosterone levels were sampled only at one time point after the initiation of exposure to drug, it is yet to be determined whether similar differences would be obtained after other doses and at other time points. Nevertheless, these results demonstrate that the active (response contingent) vs. passive (response noncontingent) administration of cocaine can differentially affect the activation of the hypothalamo–pituitary–adrenal axis, and suggest that this type of experimental design might prove useful in delineating the relationship between the activation of the hypothalamo–pituitary–adrenal axis and the reinforcing effects of cocaine.

Acknowledgements

Supported by NIH/NIDA grant DA10830 and a grant from the LSUHSC Neuroscience Center. C.P.F. is supported by a Research Scientist Development Award from NIDA (DA00211). Portions of these data were presented at the EBPS meeting 1996, Cagliari, Italy. We are very grateful to Ms. V.A. Kenigs for technical assistance.

References

Borowsky, B., Kuhn, C.M., 1991. Monoamine mediation of cocaine-induced hypothalamo–pituitary–adrenal activation. J. Pharmacol. Exp. Ther. 256, 204–210.

Calogero, A.E., Gallucci, W., Kling, M.A., Chrousos, G., Gold, P.W., 1989. Cocaine stimulates rat hypothalamic corticotropin-releasing hormone secretion in vitro. Brain Res. 505, 7–11.

Deroche, V., Piazza, P., Casolini, P., Le Moal, M., Simon, H., 1993. Sensitization to the psychomotor effects of amphetamine and morphine induced by food restriction depends on corticosterone secretion. Brain Res. 611, 352–356.

Dworkin, S.J., Co, C., Smith, J.E., 1995a. Rat brain neurotransmitter turnover rates altered during withdrawal from chronic cocaine administration. Brain Res. 682, 116–126.

Dworkin, S.J., Mirkis, S., Smith, J.E., 1995b. Response-dependent versus response-independent presentation of cocaine: differences in the lethal effects of the drug. Psychoneuropharmacology 117, 262–266.

Emmett-Oglesby, M., Peltier, R.L., Depoortere, R.Y., Pickering, C.L., Hooper, M.L., Gong, Y.H., Lane, J.D., 1993. Tolerance to self-administration of cocaine in rats: time course and dose–response determination using a multi-dose method. Drug Alcohol Depend. 32, 247–256.

Goeders, N.E., Guerin, G.F., 1994. Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. Psychopharmacology 114, 63–70.

Haney, M., Maccari, S., Le Moal, M., Simon, H., Piazza, P.V., 1995. Social stress increases the acquisition of cocaine self-administration in male and female rats. Brain Res. 698, 46–52.

Hemby, S.E., Co, C., Koves, T.R., Smith, J.E., Dworkin, S.J., 1997.

Differences in extracellular dopamine concentration in the nucleus accumbens during response-independent cocaine administration in the rat. Psychopharmacology 133, 7–16.

Krueger, R.J., Lin, C., Fung, Y.K., 1991. Effect of chronic administration of nicotine or cocaine on steroidogenesis in rat adrenocortical cells. J. Pharm. Pharmacol. 43, 200–203.

Mendelson, J.H., Teoh, S.K., Mello, N.K., Ellingboe, J., Rhoades, E., 1992. Acute effects of cocaine on plasma ACTH leutinizing hormone and prolactin levels in cocaine-dependent men. J. Pharmacol. Exp. Ther. 263, 505–509.

Pechnick, R.N., Poland, R.E., 1994. Neuroendocrine responses produced by stereoisomers of PCP/NMDA and sigma receptors ligands. Eur. J. Pharmacol. 263, 115–120.

Rivier, C., Vale, W., 1987. Cocaine stimulates adrenocorticotropin (ACTH) secretion through a corticotropin releasing factor (CRF)-mediated mechanism. Brain Res. 422, 403–406.

Saphier, D., Welch, J.E., Farrar, G.E., Goeders, N.E., 1993. Effects of intracerebroventricular and intrahypothalamic cocaine administration on adrenocortical secretion. Neuroendocrinology 57, 54–62.

Sarnyai, A., Mello, N.K., Mendelson, J.H., Nguyen, P.H., Eros-Sarnyai, M., 1995. Effects of cocaine and corticosterone-releasing factor on pulsatile ACTH and cortisol release in ovariectomized rhesus monkeys. J. Clin. Endocrinol. Metabol. 80, 2745–2751.

Wilson, J.M., Nobrega, J.N., Corrigall, W.A., Coen, K.M., Kish, S.J., 1994. Amygdala dopamine levels are markedly elevated after self — but not passive — administration of cocaine. Brain Res. 668, 39–45.